Remarks

Priority

The Examiner alleges that the concept of a pulsatile release formulation of milnacipran was first introduced in U.S.S.N. 60/431,861, which was filed on December 9, 2002, and thus the priority date for this terminology is December 9, 2002. The Examiner is incorrect. The concept of a pulsatile release formulation of milnacipran was first introduced in U.S.S.N. 60/431,627, which was filed on December 5, 2002, at least at page 4, lines 16-21; page 5, lines 3-10; and page 5, lines 15-26. Accordingly, the priority date for the current claims is December 5, 2002.

Specification

The specification was amended to reference the limitations of claims 14, 18, and 22 as requested by the Examiner and to correct grammatical errors. Support for the amendment is found, at least, in claims 14, 18, and 22 as originally filed.

Claims

Claims 1-24 are pending. Claim 1 was amended to specify that the composition produces a therapeutic effect over approximately 24 hours when administered to a patient in need thereof, with diminished incidence or reduced intensity relative to one or more immediate release milnacipran side effects. Support for the amendment is found, at least in claim 24, as originally filed. Claim 13 was amended to correct a typographical error.

The undersigned requests an interview with the Examiner in the event that this amendment and response does not place the application in condition for allowance.

Rejection Under 35 U.S.C. § 112, second paragraph

Claim 13 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Claim 13 has been amended to specify an active metabolite of milnacipran. Support for the amendment is found, at least, at page 16, lines 27-28. Accordingly, claim 13, as amended, is definite.

Rejection Under 35 U.S.C. § 102

Claims 1-9, 11-13, 15-17, 19-21, 23, and 24 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 6,699,506 to Paillard *et al.* ("Paillard"). Applicants respectfully traverse this rejection.

Paillard describes a prolonged release pharmaceutical composition, for oral administration, containing a single daily dose of 60 to 140 mg of milnacipran (abstract). Paillard does not disclose a pulsatile release formulation as required by the claims. The applicants define a pulsatile release dosage form as one that mimics a multiple dosing profile without repeated dosing and allows at least a twofold reduction in dosing frequency as compared to that drug presented as a conventional dosage form (e.g. as a solution or prompt drug-releasing, conventional solid dosage form) (page 9, lines 5-11). A pulsatile release profile is characterized by a first dose of drug that is released substantially immediately following administration, followed by a period of no release followed by release of a first, and optionally a second, delayed

release dose (page 9, lines 13-16). Pulsatile release is not the same thing as prolonged release. The compositions described in Paillard continuously release drug over an extended period of time (*see* Figures 1-3 of Paillard). Paillard does not disclose or suggest a formulation characterized by rapid drug release followed by a period of no release, followed by release of a first, and optionally second, delayed release dose as required by claim 1 and the claims dependent thereon. Accordingly, claims 1-9, 11-13, 15-17, 19-21, 23, and 24 are novel over Paillard.

Rejection Under 35 U.S.C. § 103

Claims 1-13, 15-17, 19-21, 23, and 24 were rejected under 35 U.S.C. § 103(a) as obvious over Paillard, in view of U.S. Patent No. 7,008,640 to Watanabe *et al.* ("Watanabe"). Claims 1-13, 15-21, 23, and 24 were rejected under 35 U.S.C. § 103(a) as obvious over Paillard, in view of Menza *et al.* (*J. Clin. Psychiatry*, 61(5), 378-81, (2000)) ("Menza"). Claims 1-13, 15-17, and 19-24 were rejected under 35 U.S.C. § 103(a) as obvious over Paillard, in view of Ansseau *et al.* (*Psychopharm.*, 114, 131-137, (1994)) ("Ansseau"). Applicants respectfully traverse this rejection.

Paillard in view of Watanabe

a. Paillard

As discussed above, Paillard does not disclose or suggest a pulsatile release milnacipran formulation.

b. Watanabe

Watanabe describes a pharmaceutical composition for oral use containing a drug, an aminoalkyl methacrylate copolymer E, and an acidic substance (abstract).

The Examiner alleges that Watanabe discloses pulsatile release formulations. The Examiner is incorrect. Watanabe cites U.S. Patent Application Publication No. 2002/0028240 to Sawada *et al.* ("Sawada") as disclosing pulsatile-release compositions. The compositions described in Sawada are delayed release compositions not pulsatile release compositions as defined in applicants' specification, which produces at least a two-fold reduction in dosing frequency. Delayed release compositions are characterized by a period of no release followed by sustained release of the drug (abstract). In contrast, as discussed above, pulsatile release compositions are characterized by a first dose of drug that is released substantially immediately following administration, followed by a period of no release (lag time), followed by release of one or more delayed release doses.

Watanabe does not disclose or suggest a pulsatile release formulation of milnacipran that produces a therapeutic effect over approximately 24 hours when administered to a patient in need with diminished incidence or reduced intensity relative to one or more immediate release milnacipran side effects. Watanabe is concerned with trying to improve absorption by increasing drug permeability of the digestive tract mucous membrane and/or the mucous layer distributed over this membrane. Milnacipran is rapidly absorbed in the GI tract, typically from 0.05 to 4 hours. Increasing the rate of absorption of milnacipran is likely to exacerbate the side effects

associated with milnacipran administration. Watanabe is silent regarding diminishing the incidence or reducing the intensity of one or more milnacipran immediate release side effects. In fact, Watanabe does not even discuss the side effects associated with milnacipran. The claimed compositions provide better patient compliance since they are administered once a day and are also better tolerated by patients because the divided dosage should diminish the incidence and/or reduce the intensity of one or more milnacipran immediate release side effects.

c. One of ordinary skill in the art would not be motivated to combine Paillard and Watanabe to arrive at the claimed compositions

As discussed above, neither Paillard nor Watanabe disclose or suggest a pulsatile release composition of milnacipran. Further, neither Paillard or Watanabe discloses or suggests a pulsatile release composition of milnacipran that produces a therapeutic effect over approximately 24 hours when administered to a patient in need, with diminished incidence or reduced intensity relative to one or more immediate release milnacipran side effects. Watanabe is concerned with trying to improve absorption by increasing drug permeability of the digestive tract mucous membrane and/or the mucous layer distributed over this membrane, not diminishing the incidence or reducing the frequency of milnacipran side effects. As discussed above, increasing the rate of absorption of milnacipran is likely to exacerbate the side effects associate with milnacipran administration. Accordingly, one of ordinary skill in the art would not be motivated to substitute or combine the prolonged release composition of Paillard with the delayed release compositions of Watanabe to arrive at the claimed compositions. Even if one of

ordinary skill in the art were motivated to combine the references, Watanabe does not provide the elements missing from Paillard. Accordingly, claims 1-13, 15-17, 19-21, 23, and 24 are not obvious over Paillard in view of Watanabe.

Paillard in view of Menza

a. Paillard

As discussed above, Paillard does not disclose or suggests a pulsatile release milnacipran formulation.

b. Menza

Menza describes administering modafinil to augment a partial or nonresponse to an antidepressant (abstract). Menza does not disclose or suggest administering modafinil in combination with a pulsatile release milnacipran formulation as required by claim 1 and the claims dependent thereon.

c. One of ordinary skill in the art would not be motivated to combine Paillard and Menza to arrive at the claimed compositions

As discussed above, neither Paillard nor Menza discloses or suggest pulsatile release milnacipran release formulations. Further, neither Paillard nor Menza discloses or suggests a pulsatile release composition of milnacipran that produces a therapeutic effect over approximately 24 hours when administered to a patient in need, with diminished incidence or reduced intensity relative to one or more immediate release milnacipran side effects. Accordingly, one of ordinary skill in the art would not be motivated to combine the prolonged

release composition of Paillard with the compositions of Menza to arrive at the claimed compositions. Even if one of ordinary skill in the art were motivated combine these references, Menza does not provide the elements missing from Paillard. Accordingly, claims 1-13, 15-21, 23, and 24 are not obvious over Paillard in view of Menza.

Paillard in view of Ansseau

a. Paillard

As discussed above, Paillard does not disclose or suggest a pulsatile release milnacipran formulation.

b. Ansseau

Ansseau describes a study comparing milnacipran (100 mg/day) and fluoxetine (20 mg/day) (abstract). Milnacipran and fluoxetine were administered once a day in the evening (page 132, 1st paragraph). Ansseau does not disclose or suggest a pulsatile release milnacipran formulation.

*c. **One of ordinary skill in the art would not be motivated to combine Paillard and Ansseau to arrive at the claimed compositions***

As discussed above, neither Paillard nor Ansseau discloses or suggest pulsatile release milnacipran release formulations. Further, neither Paillard nor Ansseau disclose or suggest a pulsatile release composition of milnacipran that produces a therapeutic effect over approximately 24 hours when administered to a patient in need, with diminished incidence or reduced intensity relative to one or more immediate release milnacipran side effects.

Accordingly, one of ordinary skill in the art would not be motivated to combine the prolonged release composition of Paillard with the compositions of Ansseau to arrive at the claimed compositions. Even if one of ordinary skill in the art were motivated combine the references, Ansseau does not provide the elements missing from Paillard. Accordingly, claims 1-13, 15-21, 23, and 24 are not obvious over Paillard in view of Ansseau.

Double Patenting Rejection

Claims 1-9 and 11-24 were provisionally rejected under statutory type double patenting as being unpatentable over claims 1-4 and 10-28 of U.S.S.N. 11/192,697 ("the '697 application"). Claims 1-3, 6-18, and 20-24 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 6-18, and 20-24 of U.S.S.N. 10/691,936 ("the '936 application"). Claim 14 was rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 9, 12, and 14-17 of U.S. Patent No. 7,038,085 ("the '085 patent"). Applicants respectfully traverse this rejection.

The '697 Application

The applicants will cancel and/or amend the conflicting claims in the '697 application once the present claims are in condition for allowance.

The '936 Application

The claims of the present application, as amended, are directed to a milnacipran formulation that provides pulsatile release of milnacipran to produce a therapeutic effect over

approximately 24 hours when administered to a patient in need, with diminished incidence or reduced intensity relative to one or more immediate release milnacipran side effects. In contrast, the claims of the '936 application are directed to a delayed release or extended release formulation of milnacipran.

The Examiner alleges that the term "extended release dosage form" as defined in the '936 application is within the scope of the definition of the term "pulsatile release dosage form", which is found on page 16 of the present application. The Examiner is incorrect. The Examiner appears to have looked at only part of the definition of pulsatile release. A "pulsatile release dosage form", as defined on page 16 of the specification, refers to a form that (1) mimics a multiple dosing profile without repeated dosing and (2) allows at least a two-fold reduction in dosing frequency as compared to that drug presented as a conventional dosage form. The passage on page 16 goes onto state that a pulsatile release profile is characterized by a time period of no release (lag time) followed by rapid drug release. On page 8, lines 24-25, the specification discloses that the compositions are characterized by an initial rapid release of a therapeutically effective dose of milnacipran followed by so-called "delayed release" pulses such that a second and optional third delayed dose of the active agent are released from the dosage form. If a third dose is incorporated into the form, it is released after a period of no release (lag time) following release of the second dose. These delayed release pulses can be released immediately or can be released over an extended period of time. This definition does not encompass delayed release or extended release formulations, neither of which have an initial

rapid release of a therapeutically effective dose of milnacipran, followed by a period of no release (lag time), followed by "delayed release" pulses such that a second and optional third delayed dose of the active agent is released from the dosage form. Accordingly, claims 1-3, 6-18, and 20-24 are not obvious in view of claims 1-3, 6-18, and 20-24 of the '936 application.

The '085 Patent

Claim 14 of the present application depends from claim 1 and is directed to a milnacipran formulation that provides pulsatile release of milnacipran to produce a therapeutic effect over approximately 24 hours when administered to a patient in need, with diminished incidence or reduced intensity relative to one or more immediate release milnacipran side effects, wherein the milnacipran is in the form of a therapeutically equivalent dose of para-hydroxy-milnacipran (F2782) or pharmaceutically acceptable salts thereof.

A comparison of claim 14 and the claims of the '085 patent is shown in the table below:

Claim 14 of the present application	Claims of the '085 patent
1. A milnacipran formulation that provides pulsatile release of milnacipran to produce a therapeutic effect over approximately 24 hours when administered to a patient in need, with diminished incidence or reduced intensity relative to one or more immediate release milnacipran side effects. 14. The milnacipran formulation of Claim 1, wherein the milnacipran is in the form of a	1. An isolated compound represented by A (*see* claim 1 of the '085 patent for the structure of A). 2. An isolated compound represented by B (*see* claim 2 of the '085 patent for the structure of B). 3. The compound of claim 1 or 2, wherein X represent O. 9. A formulation, comprising a compound of

therapeutically equivalent dose of para-hydroxy-milnacipran (F2782) or pharmaceutically acceptable salts thereof.	claim 1 or 2; and a pharmaceutically acceptable excipient. 12. A method of treating a mammal suffering from depression, comprising the step of administering to the mammal a therapeutically effective amount of an isolated compound represented by A (*see* claim 12 of the '085 patent for the structure of A). 14. A method of treating a mammal suffering from mental disorders including Functional Somatic Disorders, for example, depression, fibromyalgia syndrome, chronic fatigue syndrome, pain, attention deficit/hyperactivity disorder, and visceral pain syndromes (VPS), such as irritable bowel syndrome (IBS), noncardiac chest pain (NCCP), functional dyspepsia, interstitial cystitis, essential vulvodynia, urethral syndrome, orchialgia, and affective disorders, including depressive disorders (major depressive disorder, dysthymia, atypical depression) and anxiety disorders (generalized anxiety disorder, phobias, obsessive compulsive disorder, panic disorder, post-traumatic stress disorder), premenstrual dysphoric disorder, temperomandibular disorder, atypical face

	pain, migraine headache, and tension headache, comprising the step of: administering to said mammal a therapeutically effective amount of an isolated compound represented by A (*see* claim 14 of the '085 patent for the structure of A). 15. The method of claim 12, 13, or 14, wherein the mammal is a primate, equine, canine, or feline. 16. The method of claim 12, 13, or 14, wherein the mammal is human. 17. The method of claim 12, 13, or 14, wherein the compound is administered orally.

Claim 14 depends from claim 1 and requires that the formulation is a pulsatile release formulation. None of the claims in the '085 patent cited by the Examiner are directed to a pulsatile release formulation. The Examiner alleges that the rejection is proper because the '085 patent discloses that the formulation may comprise an immediate release portion in combination with an extended release portion. The Examiner has not applied the correct standard for a double patenting analysis.

In determining whether a nonstatutory basis exists for a double patenting rejection, the first question to be asked is — does any claim in the application define an invention that is merely an obvious variation of an invention claimed in the patent? Obviousness-type double

patenting requires rejection of an application claim when the claimed subject matter is not patentably distinct from the subject matter claimed in a commonly owned patent, or a non-commonly owned patent but subject to a joint research agreement as set forth in 35 U.S.C. 103(c)(2) and (3), when the issuance of a second patent would provide unjustified extension of the term of the right to exclude granted by a patent. See *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 58 U.S.P.Q.2d, 1869 (Fed. Cir. 2001); *Ex parte Davis*, 56 U.S.P.Q.2d 1434, 1435-36 (Bd. Pat. App. & Inter. 2000).

Any obviousness-type double patenting rejection should make clear: (A) The differences between the inventions defined by the conflicting claims — a claim in the patent compared to a claim in the application; and (B) The reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim at issue would have been an obvious variation of the invention defined in a claim in the patent. **When considering whether the invention defined in a claim of an application would have been an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art.** *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1279, 23 U.S.P.Q.2d 1839, 1846 (Fed. Cir. 1992).

The Examiner is attempting to use the specification of the '085 patent as prior art. None of the claims of the '085 patent are directed to a pulsatile release formulation of milnacipran. A pulsatile release formulation, as described in the applicants' specification, is characterized by an initial rapid release of a therapeutically effective dose of milnacipran, followed by a period of no

release (lag time), followed by "delayed release" pulses such that a second and optional third delayed dose of the active agent is released from the dosage form. None of the claims of the '085 patent are directed to a pulsatile release formulation of milnacipran that produce a therapeutic effect over approximately 24 hours when administered to a patient in need, with diminished incidence or reduced intensity relative to one or more immediate release milnacipran side effects. Accordingly, claim 14 is not obvious over claims 1-3, 9, 12, and 14-17 of the '085 patent.

Allowance of claims 1-24, as amended, is respectfully solicited.

Respectfully submitted,

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